Post -Renal Transplant Tuberculosis:Clinical Presentation & Outcome

MMJ 2010; 9: 1-6

Nidham A. Jaleel

C.A.M.B. FRCP-Lond., FRCP-Edin., Ass. Professor, Dept. of Medicine, Al-Mustansiriya College of Medicine

Abstract:

Background: Tuberculosis is increasing in Iraq population since 1980s. Studies from the surrounding countries showed that renal transplant recipients are more liable for TB infection.

Aim: To study the clinical presentation and outcome post renal transplant tuberculosis.

Patient and Methods: 412 recipients are enrolled from May 2001 till November 2008. Age, gender, weight, waiting list duration, period between TB infection and transplant, history rejection. Investigation as blood urea, s.creatinine, hemoglobin, ESR, blood sugar, are recorded at time of TB diagnosis and at end of TB treatment. Diagnosis of TB depends on clinical finding supported by bacteriological, radiological, and/or hispothological.

Results: there are 18 (4.37%) PTTB cases (12 pulmonary, six extrapulmonary) are recorded. None of them has a history of TB, nor a radiological finding suggestive of TB at time of transplant. All these cases are HIV –ve. Most cases have been diagnosed within the first year of transplantation. Fever is present in 17/18 patients, mostly low grade fever. Diabetes 3/18 cases and history of acute rejection is 6/18 patients. Mortality was 5/18 (27.77%). Acute rejection and diabetics are strong associations. Renal impairment at time of TB diagnosis significantly associated with high mortality.

Conclusion: PTTB is high, and pulmonary TB is also the most common type here. When it is compared with immun-competent TB cases, there is an increase in percentage of extra-pulmonary TB.

Introduction:

The incidence of tuberculosis (TB) in Iraq has been increased progressively in the last 25 years & according to WHO reports , it was (1%) in 1978 & (1,7%) in 1995, while in year 2000 it was increased up to (2,7%) [1, 2].

The economic sanction, imposed on Iraq since 1990 till 2003, had a direct effect on increasing TB incidence in general population. After US-invasion of Iraq in 2003, the situation has been worsen due to destruction of the infrastructures in the country leading to serious affection of all health services including TB treatment program, particularly among vulnerable populations [2].

Renal transplantation program was seriously affected by embargo and US- invasion. The national kidney transplant program was totally blocked for certain time after invasion, but now it is recovered in three main centers, two in Baghdad, the capital, and one in Erbil (Kurdistan region) [3].

Worldwide the incidence of tuberculosis in post-renal transplant recipients (PTTB) varies from (0.5 to 1%) in USA, (1 to 4 %) in Northern Europe, (4.5 %) in South Africa, and (11.5 %) in India [4].

According to a large study in UK, only (11) patients out of (633) patients (1.7 %) having successful renal transplantation, had developed PTTB [4]. In another study from Saudi Arabia, (14) out of (403) renal transplant recipients (3.5%) had PTTB. Most of the PTTB cases were encountered in the first year following kidney transplantation [5].

Reactivation of latent infection is believed to be the predominant mechanism for development of active tuberculosis after transplantation [6,7, 8]. In published series, information about pre-transplantation tuberculin test status is available for fewer than half of organ transplant patients who developed active tuberculosis after transplantation. Among this subgroup, only 22% demonstrate a positive response. There is a high false negative rate due to multiple factors present in patients with chronic organ dysfunction. In addition, only 5% of transplant recipients

with tuberculosis have a pre-transplantation history of infection, while only 12% demonstrate chest radiographic evidence of prior infection and less common modes of acquisition including nosocomial outbreaks and donor transmission through infected allograft [4].

In Iraq, because of low sensitivity of tuberculin skin test which was mentioned above, and the obligatory use of BCG for all new born infants [2], the tuberculin skin test is not that one of the standard practice in the preparation of patient for transplant, nor for diagnosis of latent infection after transplantation.

To reduce the rate of PTTB; an Indian double blind randomized controlled trial had studied the prophylactic use of isoniazed (INH) in renal transplant recipients. Accordingly; INH prophylaxis nine months after transplantation was considered highly suggestive[7].

Literature review showed that management of PTTB dose not differ from other tuberculus patients, but drugs & dose modification may be needed to avoid drug interaction with the immunosuppressive drugs. The optimum duration of anti-TB treatment is not well defined, and in most centers the treatment is given for a minimum period of one year, and may be extended for 18 months[7, 8].

In Iraq, most of the cases receive four drugs (but some time three drugs) for first two months and then continue on two drugs for nine months [1, 2].

There are few TB-cases among Iraqi studies assessed renal transplant complications and outcome in general[9, 10, 11]. This work will be the first paper, for my knowledge, that studies PTTB in study the prevalence, clinical characters and outcome of tuberculosis in kidney transplant recipients, in Iraqi sample.

Patients and Methods:

The data of (412) kidney allograft recipients from 2001 – 2008 in Al-Karama kidney transplant center, and the Iraqi Kidney transplant Center, have been analyzed, and those who developed PTTB are enrolled in this study.

The males in our study are (72.2%) while the females incidence are (27.8%) & the age of the patients at time of transplantation vary from (18 – 44) years.

The patient's parameters studied include age, sex, body mass index(BMI), blood urea, creatinine clearance (by Cockcroft-Gualt's equation) , fasting blood sugar, hemoglobin, ESR, white blood cells (WBCs). All these parameters are estimated at time of diagnosis of tuberculosis and at the end of treatment. It also includes type of immunosuppressant, pre-transplant dialysis period, type of dialysis, episode of acute rejection, and type of anti-rejection regime used.

The clinical presentation of our PTTB patients is classified to pulmonary and extra-pulmonary TB, while the anti-TB drugs, duration of therapy and outcome of the disease are determined. Weight loss is considered significance, when there is (5%) loss of body weight within (12) months.

Student (t) test is used in statistical analysis of the collected data and p-value (< 0.05) is considered statistically significant.

Result:

There are 412 renal allograft recipients attending outpatient clinic in Al-Karama and the Iraqi transplant centers (304 males, and 108 females). Eighteen of them have developed PTTB, 13 male (72.3%) and five female (27.8%) (Table -1).

Pulmonary TB is the commonest form in this group & table-1 shows the patient's characters & the methods of diagnosis of the disease in the group. The radiological finding, in 13 cases (12 pulmonary + one miliary), are supported by clinical diagnosis and response to treatment (12 cases) and also by either sputum positive AFB (two cases), or pleural aspirate suggestive of TB (four cases), or pleural biopsy diagnosing TB granuloma (three cases). The remaining extra pulmonary

cases (five cases) are diagnosed by finding the TB-granuloma on tissue histopathological examination.

All the 18 patients are receiving cyclosporine, and prednisolone (table-1). Seventeen patients are receiving a third immune-suppressive drug (azothioprine in 14 cases, mophetile mycophenolate in 3 cases). None of them has received tacrolimus or sirolimus.

Regarding anti-TB treatment (Table-1), nine patients have received four drug regimens [rifampicin, ionized (INH), ethambitol (Etib) and pyrizinamide (PZA)]. While remaining nine cases have received rifampicin, INH and either Etib or PZA. For those who are receiving a three-drug regimen, Etib (three patients) is used for those with normal kidney function, while PZA (six patients)is used in case of renal impairment. None of the 18 cases has received streptomycin. The total duration of treatment for those who recovered was at least nine months.

Complete recovery is noticed in 13 patients (72.22%) and death in five patients with a mortality rate of (27.77%) (Table-1). Most of the death have encountered during the first two month of treatment.

Acute allograft rejection at any time following transplantation has been found in six cases (33.3%). The outcome of management of these PTTB cases, whether they recovered or died (Table-2) is not affected by age, waiting list duration, and post-transplant period. It is significantly affected by the creatinine clearance at time of diagnosis; which plays an important roll in the outcome (P 0.048) and over-weight (BMI) at diagnosis which also increases significantly the mortality rate (P 0.012). Those who have recovered, have a normal body mass index.

Gender, type of immunosuppressant, and clinical type of TB has no significant effect on outcome ($P > 0.05$) (Table-3). The presence of acute rejection at anytime following renal transplant (Table-3) significantly affects the outcome (P 0.009) of PTTB.

The clinical characters of PTTB at time of diagnosis in our patients are shown in table -4.

Discussion:

The prevalence of tuberculosis in renal transplant recipients, in any country will reflect the endimicity of TB in that country [9, 10, 11]. The presence of (18) PTTB patients (4.37%) among the studied renal allograft recipients (table-1) points out that PTTB is not rare in Iraq & needs a lot of measures to prevent it and to have early diagnosis of the disease since it has already high prevalence in general population in Iraq. This figure (4.37%) is found to be less than that found in India (9.5-14.7 %) [12] and comparable to that found in Spain (4.2%) ,Turkey (4.15%) & south Africa (4.5-4.9%) while less than that found in Germany (1%), UK(1.7%) , Europe (2-3.1 %) [12] and Iran (2%) [13].

Table -1: The Clinical Characters of Post RT-TB Patients

			No	%	
Gender	**Female**		**5/108**	**27.8**	**P > 0.05**
	Male		**13/304**	**72.2**	
Type of Tuberculosis	**Pulmonar**	**Pulmonary tuberculosis**	**7**	**38.9**	**66.66**
		Pulmonary lesion with Pleural effusion	**2**	**11.1**	
		Tuberculus Pleural effusion alone	**3**	**16.7**	
	Extra pulmonary	**Miliary Tuberculosis**	**1**	**5.6**	**33.33**
		Scrotal cellulites	**1**	**5.6**	
		Cervical Lymph Nodes	**2**	**11.1**	
		Epididymo-orchitis	**1**	**5.6**	
		Laryngitis	**1**	**5.6**	
Method of Diagnosis	**CXR[#]+ Sputum AFB* positive + Clinical**		**2**	**11.1**	
	CXR + Clinical (including one miliary)		**7**	**38.8**	
	CXR + Pleural Aspirate + Pleural biopsy		**3**	**16.6**	
	Pleural Aspirate + Clinical		**1**	**5.26**	
	Tissue Biopsy (other than pleural biopsy)		**5**	**27.7**	
History of Acute rejection	**Yes**		**6**	**33.3**	
	No		**12**	**66.7**	
Immuno- suppression	**Cyclosporine + Azothioprine + Prednisolone**		**14**	**77.8**	
	Cyclosporine + Mycophenolate + Prednisolone		**3**	**16.7**	
	Cyclosporine + Prednisolone		**1**	**5.6**	
Anti-TB Drugs	**Rifadin, INH, Ethambitol and Pyrizinamide**		**9**	**50.0**	
	Rifadin, INH, and Pyrizinamide		**6**	**33.3**	
	Rifadin, INH, and Ethambitol		**3**	**16.7**	
Outcome	**Recovery**		**13**	**72.2**	
	Death		**5**	**27.8**	

(CXR = chest x-ray); * (AFB = Acid-Fast Bacilli)

Table -2 Characters of tuberculus patients according to treatment outcome

Clinical parameter	Outcome			P value
	Death	Recovery	Total	
Age (years)	30.80±9.01 (21.00-44.00)	28.08±6.97 (18.00-42.00)	28.83±7.41 (18.00-44.00)	0.502
Waiting list time (month)	2.80±2.17 (1.00-6.00)	5.85±6.04 (2.00-24.00)	5.00±5.37 (1.00-24.00)	0.295
Post transplantation period (month)	13.20±9.50 (2.00-25.00)	14.15±15.65 (1.00-56.00)	13.89±13.94 (1.00-56.00)#	0.901
BMI (Kg/m2) at TB diagnosis	27.16±1.67 (24.40-28.70)	22.53±3.44 (17.20-27.60)	23.82±3.68 (17.20-28.70)	0.012*
Creatinine clearance at diagnosis of TB	50.40±49.95 (16.00-138.00)	92.31±31.76 (27.00-129.00)	80.67±40.89 (16.00-138.00)	0.048*

All the patient are below 12 months except one (laryngeal TB) has 56 months post transplant period.

*Significant at 0.05 level of significance using t-test for two independent means

Table -3 Factors affecting out come of anti-TB treatment

Character		Outcome				P value
		Death		Recovery		
		No	%	No	%	
Gender	Female	2	40.0	3	60.0	0.473
	Male	3	23.1	10	76.9	
Immuno-suppression	C+AZA+P	3	21.4	11	78.6	0.231
	C+M+P	2	66.7	1	33.3	
	C+P	-	-	1	100	
Type of TB	Pulmonary	4	22.2	8	78.8	0.524
	Exterapulmonary	1	16.7	5	83.3	
Type Anti-TB	RIE	1	33.3	2	66.7	0.871
	RIEP	2	22.2	7	77.8	
	RIP	2	33.3	4	66.7	
Acute rejection	No	1	8.3	11	91.7	0.009*
	Yes	4	66.7	2	33.3	

#1 (C=Cyclosporine, AZA=azothioprine, P=Prednisolone, M=Mycophenolate)

#2 (R=rifampicin, I=INH, E=Ethambitol, P=Pyrizinamide)

*Significant at 0.05 level of significance using Pearson chi-square test.

Table-4 Other Clinical features of PT-TB

Clinical feature	Number of patients	%
Presence of BCG vaccine scar	18	100
HIV negative (ELISA)	18	100
Past medical history of TB	Non	Non
Radiological pre-transplant TB	Non	Non
Wt loss	5	29.41
ESR $\geq$ 80 mm/h	5	23.52
Diabetes (pre & post-transplant)	3	17.64
Fever	17	97.7
Cough	8	47.05
Pleural pain	5	29.41
Ccl <50 ml/min (at diagnosis)	6	33.33

Concerning gender in our study, number of male recipients are found to be more than female as it is seen in (Table -1) & this is proved to have no significant statistical difference (P value > 0.5) [8,9,10].

Usually tuberculosis occurs after six months of renal transplantation [12] and this fact goes with our results where all our cases were detected during the first year of transplantation. Pulmonary tuberculosis with or without pleural effusion was the most common presenting clinical form (66%) in our study (Tab- I) an this is more or less close to the result of Turkish study (54%)[14], while the exdtra-pulmonary TB constitutes about (33.3%) .This figure also indicates that the incidence of pulmonary TB is close to its incidence in general population (71.4%) [2,8]. More over our results found to be comparable to the results reported by Al-taee & Al-shammaa [10] where the prevalence of PTTB was found to be (3.3%) & mostly of pulmonary form (only one extra pulmonary form).

According to table-1, there were one case per scrotal, miliary, epididemal, & laryngeal TB of the extra pulmonary types, while only two cases had cervical tubercular lymphadenitis.

The follow-up period of our cases was ranging (1–56) months with a mean of (13.89±13.94) months (table-2). But as it is seen in the subtitle (#) of that table, most has occurred within the first year except one case (laryngeal TB) occurred after 56 months of transplant. This make the range wide and the SD is wide also. The early development of TB in patients receiving cellcept & tacrolimus may be significant because of higher level of immunosuppression & higher risks of concomitant medical problems during the first six months after transplantation [14, 15].

Six of our patients (33.3%) had history of an attack of acute rejection treated by conventional pulse steroid therapy successfully (table-1).This is similar to the results reported by Alaattin et.al [15] and Fishman[16]. The most probable explanation for this rejection is , the use of aggressive immune-suppression during rejection that may cause injury to immune system [12].

The mortality rate (27%) in our cases is close to the result (30%) mentioned by Paolo et al [17] and also by Robin Patel & Carlos Paya[18].

Concerning the outcome of TB, treatment has no significant relation to age, duration of the waiting list & post renal transplant period, while mortality has significant relation with the impairment of creatinine clearance at time of diagnosis & those patients who have died during treatment period have significantly lower creatinine clearance at the biging of treatment (table-2)

and nowadays this become a well known fact that renal impairment itself causes high mortality rate[18].

Over weight and the high body mass index (BMI) carry a worse prognosis (Table-2) probably because of its negative effects on cardiac & renal functions & higher incidence of diabetes mellitus.

Conversion of immunosuppressant from azothioprine to cellcept in our studies doesn't shows any increase in the incidence of PTTB, while in other studies the conversion was associated with increased incidence of tuberculosis because of the potency of the used immunosuppressive. This difference can be related to the under use of cellcept in our patients, because of being costly and didn't been used by most of our recipients in this study.

Conclusion:

PTTB is a problem among kidney transplant population in Iraq .It is one of the causes of morbidity & mortality in renal transplantation population. So pre & post renal transplant screening for TB is essential in Iraq & the earlier the diagnosis is the better is the prognosis.

Pulmonary TB is still the commonest type of PTTB while extra pulmonary TB, although is less common, but still has higher incidence than in general population.

In our series most of PTTB cases are encountered in the first year following kidney transplantation & has direct & significant statistical relationship with the episode of acute rejection.

Type of immunosuppressant has no effect on the out come of the disease in our patients (but this result need further reevaluation because of limited number of studied cases that changing their immunosuppressive drugs) while the presence of renal impairment at time of diagnosis will carry a high mortality rate in the outcome of the disease.

References

1- Dhafer S Hashim, Simon W Wartan, [Arabic language-Guide Lines in the Iraqi National program for eradication of tuberculosis]: Iraqi Anti-TB Society and Chest disease Baghdad in calibration with MOH and WHO; 3rd Edition 2007:7-8.

2- Qassim A J Salih, Flaih M H Zubaidi, Strategic Plan for TB Control in Iraq, Iraqi Anti-TB Society and Chest disease Baghdad in calibration with MOH and WHO; 2007 : 3-12.

3- Iraqi Society of Nephrology – Annul report 2007- The Second CME congress –MOH publications, Iraq-Baghdad 2007.

4- Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid organ transplant recipients: impact and implications for management. Clin Infect Dis 1998;27:1266–1277.

5- Magdi Hussein and Jacob Mooij, Tuberculosis and Chronic Renal Disease. Saudi J Kidney Dis Transplant 2002;13(3):320-330

6- Laura Passalent, Kamran Khan, Robert Richardson, Jun Wang, Helen Dedier, and Michael Gardam. Detecting Latent Tuberculosis Infection in Hemodialysis Patients: A Head-to-Head Comparison of the T-SPOT.TB Test, Tuberculin Skin Test, and an Expert Physician Panel. ISSN: 1555-9041/201–0068

7- M. Moghadammi, Fever in Transplant Recipient, A Practical Approach, Shiraz E-Medical Journal recipients in India. Transplantation 1996, 61: 2 211-5.]

8- Sakhuja V , Jh A, Vovarma PP . The high incidence of tuberculosis among renal transplant, Transplantation. 61(2):211-215, January 27, 1996

9 - Raidh A. Saigh Chest infection in kidney transplant recipients. Kufa Med.Journal.2006. 9: 289 - 303

10 - Iqdam K. Sh. Al-Taee, Ihsan AlShamaa. Long Term Follow up of Renal Transplant patients –A Single Centre Experience in Iraq. Saudi Journal if Kid Dis. 2005; 16(1):40-45
11-Wael Latif Jabur. Hareth M. Mohammad Saaed . Khlid Abdulla. Early Non-Immune Post-Renal Transplant Complication: A single center Experience. Saudi Journal if Kid Dis. 2008; 19(8):651- 657 .
12- Paulose P Thomas. Post-Transplant Tuberculosis.Saudi J kidney Dis Transplant, 2002-13(4):445-450
13- G. Pourmand, S. Salem, A. Mehrsai, M. Taherimahmoudi, R. Ebrahimi, M.R. Pourmand Infectious complications after kidney transplantation: a single-center experience; Transplant; Infectious Disease. Volume 9 Issue 4, Pages 302 – 309. Published Online: 19 May 2007
14- Sayiner, Abdullah; Ece, Turhan; Duman, Soner; Yildiz, Alaattin; Özkahya, Mehmet; Kiliçaslan, Zeki; Tokat, Yaman. Tuberculosis in renal transplant recipients, Transplantation:Volume 68(9)15 November 1999pp 1268-1271
15- Alaattin Yildiz, Mehmet Sukuri, Ayd Turkmen, etal. Tuberculosis after renal transplantation: experience of one Turkish centre. Nephrol Dial Transplant (1998) 13: 1872–1875
16- Jay A. Fishman. Infection in Solid-Organ Transplant Recipients. NEJM. 2007. 357:2601-2614
17- Paolo Cravedi, Marina Noris, and Giuseppe Remuzzi. Report of the First World Transplant Congress Clin J Am Soc Nephrol 2: 393–400, 2007
18- Robin Patel, carlos V Paya. Infections in Solid-Organ Transplant Recipients. Clinical Microbiology Review ;American Society for Microbiology Jan 1997Vol. 10, No. 1 , p. 86–124